REMARKS

This Amendment, filed in reply to the Office Action dated January 30, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 14-21 are rejected. Claim 14 is amended herewith to recite a solution-type antibody preparation comprising an antibody, and an effective amount of glycine and citric acid to suppress soluble association of the antibody, chemical degradation of the antibody, and insoluble aggregation of the antibody. Support for the amendment can be found throughout the specification as originally filed, and at, for example, in the paragraph bridging pages 3 and 4.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Information Disclosure Statement

Applicants thank the Examiner for returning an initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed December 29, 2008, indicating consideration of the references therein.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority, and for acknowledging receipt of a certified copy of the foreign priority document, namely JP 2003-343645.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing all the rejections previously of record.

Claims 14-21 are Definite under 35 U.S.C. § 112, second paragraph

On page 2 of the Office Action, Claims 14-21 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

In making the rejection, the Examiner asserts that recitation of "suppress formation of a soluble solution" renders the claim indefinite as it is unclear how a solution-type antibody solution, as claimed, may be produced.

Solely to advance prosecution, Applicants herewith amend Claim 14 to recite "[a] solution-type antibody preparation comprising an antibody, and an effective amount of glycine and citric acid to suppress soluble association of the antibody, chemical degradation of the antibody, and insoluble aggregation of the antibody." Applicants note that the amendment is amply supported by the specification as filed, such as in the paragraph bridging pages 3 and 4, and inherently by Example 2. Applicants respectfully submit that the amendment overcomes the rejection.

Withdrawal of the rejection is respectfully requested.

Claims 14-21 are Patentable under 35 U.S.C. § 103(a)

On page 3 of the Office Action, Claims 14-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over EP 1174148 in view of U.S. Patent Application Pregrant Publication No. 2003/0190316, of record.

In making the rejection, the Examiner contends that the '148 publication discloses an antibody formulation comprising a humanized antibody, sodium citrate and a non-ionic surfactant, citing Claims 1-8. The Examiner further contends that the '148 publication discloses that the concentration of the antibody in the formulation may be 5-50 mg/ml, citing paragraph [0008], that the pH of the preparation may range from 4.9-5.95, and that the buffer concentration may be 10mM, citing Table 1 and paragraphs [0028] and [0029].

The Examiner asserts that the '148 publication discloses that buffers may be used alone, or in combination, exemplary buffers being phosphate, citrate, acetate, tartrate, malate, and arginine, citing paragraph [0014], and Claims 6-7. The Examiner further asserts that the '148 publication discloses the addition of polysorbate in the presence of sodium citrate or sodium phosphate, citing Claim 8. The Examiner acknowledges that the '148 publication neither discloses nor suggests the addition of glycine.

In an attempt to rectify the deficiencies of the '148 publication, the Examiner cites to the '316 publication, which allegedly discloses that glycine improves stabilization and reduces aggregation, citing paragraph [0089]. The Examiner further asserts that the '316 publication discloses using a glycine concentration of 200mM, which is asserted to be equivalent to 15mg/ml.

The Examiner concludes that, at the time of the invention, one of ordinary skill in the art would readily have included glycine in the citric acid-buffered antibody solution of the '148 publication, to further improve the stability of the antibody formulation by reducing aggregation.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants respectfully disagree that one of ordinary skill in the art, having read the '148 and '316 publications, would have possessed sufficient motivation to arrive at the presently claimed invention. To the contrary, one of ordinary skill in the art would be discouraged from producing the claimed composition in view of the experimental data disclosed in the '148 publication.

Specifically, Table 1 of the '148 publication depicts the extent of antibody aggregation in acidic sodium phosphate and sodium citrate stabilization buffers. As evidenced by the data depicted in Table 1, under similar pH and temperature conditions (*i.e.*, mildly acidic pH, 60°C for 4 weeks), the level of antibody aggregation is *substantially higher* in a sodium citrate buffer than in an equivalent sodium phosphate buffer. Accordingly, one of ordinary skill in the art would instantly appreciate that the sodium citrate buffer of the '148 publication is significantly inferior for antibody stabilization vis-à-vis the sodium phosphate buffer therein, and thus would not have possessed sufficient motivation to select the sodium citrate buffer of the '148 publication for further modification to improve antibody stability. Indeed, Applicants respectfully submit that the claimed invention is not obvious at least because such a clear disclosure of inferiority would have taught one of ordinary skill in the art away from the presently claimed invention. Relevant law indicates that a reference "teaches away" when a person of ordinary skill in the art would be led in a path divergent from the path taken by the inventor. See *Monarch Knitting Mach. Corp v. Sulzer Morat Gmbh*, 139 F.3d, 877, 45 USPQ2d 1977 (Fed. Cir. 1998); *Para-Ordnance Mfg. v. SGS Importers Int'l Inc.*, 73 F.3d1085, 37 USPQ2d 1237 (Fed. Cir. 1995); and *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Clearly, one of ordinary skill in the art reading the '148 publication would not have selected the sodium citrate buffer for further modification to enhance antibody stability, when the experimental

results unequivocally demonstrate that the sodium citrate buffer is significantly inferior vis-à-vis the sodium phosphate buffer for this very purpose. For the foregoing reasons, Applicants respectfully submit that one of ordinary skill in the art would not have arrived at the presently claimed invention by following the teachings of the '148 and '316 publications, and thus a *prima facie* case of obviousness has not been established for this reason alone.

Nevertheless, even assuming *arguendo* that one of ordinary skill in the art would have possessed sufficient motivation to select the sodium citrate buffer of the '148 publication, and combine it with the glycine buffer of the '316 publication (which they clearly would not for the reasons presented above), Applicants respectfully submit that the cited references nevertheless fail to render obvious the instantly claimed composition in view of the unexpected properties possessed by the claimed composition.

Specifically, as can be seen from the data depicted in Table 3 of the specification as filed, and in the Tables in the attached Rule 132 Declaration, the claimed composition possesses the unexpected properties of superior suppression of chemical degradation, and superior suppression of soluble association of antibody. It is well-settled that a showing of an unexpected property or result, or a greater than expected result, may be sufficient to rebut a *prima facie* case of obviousness. Relevant law holds that such an unexpected result may be demonstrated by, for example, a comparison vis-à-vis the closest prior art, demonstrating unpredictability in the pertinent art area such that one of ordinary skill in the art would not expect the claimed product to possess the properties it does (See *In re May*, 197 USPQ 601 (C.C.P.A. 1978)), or demonstrating an effect greater than the sum of each the effects taken separately (*i.e.*, a demonstration of synergism). See *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989).

As discussed below, Applicants demonstrate unpredictability in the pertinent art area, such that one of ordinary skill in the art would consider the properties discovered by Applicants to be unexpected, *and* demonstrate that the claimed composition exhibits synergism with regard to the suppression of soluble association of antibody vis-à-vis antibody stabilization compositions containing citric acid or glycine alone. Applicants submit that such unexpected properties are further probative of the non-obviousness of the claimed invention, and are sufficient in themselves to rebut the rejection.

First, as evidenced by Table 9 of the specification as filed, citric acid exhibits substantially greater suppression of chemical degradation of antibody than another art-recognized antibody stabilization buffer, namely phosphoric acid buffer. In view of the state of the art, one of ordinary skill would in no way have expected citric acid to possess such superiority in inhibiting chemical degradation of an antibody, particularly in view of the experimental data in the '148 publication.

Second, Applicants respectfully refer the Examiner to the data depicted in Table 3 of the specification as filed, and the data depicted in the Tables in the attached Rule 132 Declaration. Table 3 of the specification as filed demonstrates that when phosphoric acid (Formulation 1) or citric acid (with or without mannitol; Formulations 2 and 3, respectively) is used as an antibody stabilization buffer, soluble associations of antibody are present in an amount of 0.20%-0.22% following incubation. Further, Table 2 in the attached Rule 132 Declaration demonstrates that, under the same incubation conditions, when glycine is used as an antibody stabilization buffer, soluble associations of antibody are present in an amount of 0.18% following incubation. However, when citric acid and glycine are *combined*, the amount of soluble associations of antibody only increase to 0.02% following incubation, *i.e.*, approximately ten-fold less vis-à-vis

compositions wherein glycine or citrate are present individually, but not in combination. One of ordinary skill in the art would not have predicted that combining glycine and citric acid in the same composition would have produced a synergistic reduction in the formation of soluble association of antibody by an order of magnitude vis-à-vis compositions containing either glycine or citric acid alone. There is nothing in the art that would have led one of ordinary skill in the art to have even contemplated, much less expected, such synergism. The superior property of the claimed composition to inhibit soluble antibody association is thus entirely unexpected, and is of clear practical significance, because it allows the stabilization of antibodies for extended periods whilst maximizing titer, and minimizing side effects such as fever, nausea and hypotension resulting from *in vivo* administration of soluble associations of antibody. Further, Applicants respectfully submit that such an unexpected property is commensurate with the scope of the claims, as evidenced by Tables 3 and 9, which demonstrate such superior suppression of soluble antibody association across a wide range of citric acid and glycine concentrations.

Applicants respectfully submit that one of ordinary skill in the art could not have expected that a composition containing glycine and citric acid would possess such beneficial properties, and that such is probative of the non-obviousness of the claimed invention.

Withdrawal of the rejection is respectfully requested.

2. On page 4 of the Office Action, Claim 21 is rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 1174148 and U.S. Patent Application Pregrant Publication No. 2003/0190316, as applied above in the rejection of Claims 14-20, and further in view of U.S. Patent No. 6,488,930, of record.

Because the '148 and '316 publications are relied upon for the same reasons as discussed above in the obviousness rejection of Claims 14-20, and the '930 Patent is relied upon merely for the disclosure of a humanized anti-CCR4 antibody, Applicants respectfully submit that Claim 21 is not rendered obvious for the same reasons as discussed above in response to the rejection of Claims 14-20 under 35 U.S.C. § 103(a).

3. On page 5 of the Office Action, Claim 21 is rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 1174148 and U.S. Patent Application Pregrant Publication No. 2003/0190316, as applied above in the rejection of Claims 14-20, and further in view of U.S. Patent No. 6,437,098, of record.

Because the '148 and '316 publications are relied upon for the same reasons as discussed above in the obviousness rejection of Claims 14-20, and the '098 Patent is relied upon merely for the disclosure of a humanized anti-ganglioside GD3 antibody, Applicants respectfully submit that Claim 21 is not rendered obvious for the same reasons as discussed above in response to the rejection of Claims 14-20 under 35 U.S.C. § 103(a).

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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